February 23, 1998

Director
Office of Device Evaluation (HFZ-400)

Bioresearch Monitoring Agreement for PMAs and PDPs

ODE Review Staff

Purpose

The purpose of this interoffice agreement is to provide guidance to the Office of Device Evaluation (ODE) and the Office of Compliance, Division of Bioresearch Monitoring (DBM) staff, regarding bioresearch monitoring inspections in the routine evaluation of premarket approval (PMA) applications and product development protocols (PDP). This agreement outlines the responsibilities of the PMA Staff, ODE reviewers and managers and the Office of Compliance, Division of Bioresearch Monitoring, for these programs.

Agreement

The full agreement on PMA/PDP bioresearch monitoring is embodied in the Attachment. It sets forth the respective responsibilities of the Office of Device Evaluation and the Office of Compliance.

Effective Date

This guidance is effective immediately.

Susan Alpert, Ph.D., M.D.

BIORESEARCH MONITORING AGREEMENT

Between the

OFFICE OF COMPLIANCE, CENTER FOR DEVICES
AND RADIOLOGICAL HEALTH

and the

OFFICE OF DEVICE EVALUATION, CENTER FOR DEVICES
AND RADIOLOGICAL HEALTH

Purpose

The purpose of this interoffice agreement is to provide guidance to the Office of Device Evaluation (ODE) and Division of Bioresearch Monitoring (DBM) staff regarding bioresearch monitoring audits in the routine evaluation of premarket approval (PMA) applications. This agreement outlines each office's responsibility for the PMA/DBM programs. Specifically it outlines the responsibilities of the PMA Staff, ODE reviewers and managers and the DBM within the Office of Compliance (OC). The bioresearch monitoring inspectional process is separate and distinct from the pre-approval manufacturing facility inspection process associated with the Quality System Regulation (21 CFR Part 820). The manufacturing facility inspection was the subject of Blue Book Memorandum #P91-3.

A detailed discussion of the bioresearch monitoring process is provided in Attachment A and is also available on the Internet at http://www.fda.gov/cdrh/comp/bimo.html.

Agreement

It is important for all ODE managers and reviewers to understand the impact that the bioresearch monitoring program has on the PMA and PDP evaluation process. The following ODE/DBM agreement outlines the respective roles of the ODE and DBM staff in routinely assuring the integrity of the data in PMA applications.

This agreement does not cover issues, policies and procedures that arise under the Application Integrity Policy (AIP), which is the subject of Blue Book Memorandum #I91-2, Integrity of Data and Information Submitted to ODE. The AIP includes the evaluation of potential fraud, untrue statements of material facts, bribery and illegal gratuities.

The validity of the clinical data submitted in PMAs and PDPs through routine onsite data audits must be assured through the bioresearch monitoring process. Responsibilities under this agreement are as follows.

1. The PMA Staff within the Program Operations Staff (POS) of ODE, will notify the Director, DBM within OC, via a memorandum and electronically (electronic mail or facsimile), of the receipt of an original PMA application, PDP, or panel-track supplement (hereafter known as "submission"). This action will serve to initiate interaction between the two offices.

2. DBM may conclude after consultation with the responsible ODE division that bioresearch monitoring inspection(s) are not required for the submission, e.g., a licensing agreement would not normally require such an inspection. DBM will notify POS and the reviewing division via a memorandum should such a decision be rendered.

3. The DBM Director will identify a staff member to serve as the point-of-contact for the submission. This staff member shall contact the appropriate ODE review division within 5 working days of receipt of the original PMA, PDP, or panel-track supplement. ODE shall include the DBM point-of-contact in all pertinent meetings (e.g., filing meeting), as appropriate. This early and continual communication should serve to strengthen this aspect of the review process.

4. Each ODE division will be responsible for identifying a point-of-contact method for the DBM review process. Divisions may choose to identify a central individual to coordinate the process for the division or they may choose to identify a team leader or branch chief, etc., as their preferred point-of-contact.

5. The ODE review division will be responsible for working with the DBM contact in identifying the appropriate investigational sites (e.g., clinical investigator, pre-clinical laboratory, sponsor) for potential bioresearch monitoring inspections.

6. A complete copy of the PMA will be provided to the Office of Compliance, Field Programs Branch by the Document Mail Center (DMC) upon receipt of the PMA. This copy will be shared with the DBM. The clinical portion of the PMA will be returned to the ODE DMC when the DBM has finished using that portion of the PMA. Should additional copies of the PMA be required, the bioresearch monitoring contact will be responsible for obtaining copies from the applicant or photocopying the necessary material.

7. A copy of the relevant portions of the PDP will be forwarded to DBM directly. PDP site inspections are anticipated to be completed prior to the submission of the Notice of Completion of the approved protocol.

8. The PMA Staff will provide a copy of the PMA filing decision to DBM which will also include whether CDRH has granted expedited review status to the application. DBM will take the expedited review status into account when developing, scheduling, assessing and reporting on the bioresearch monitoring inspections.

In cases where CDRH grants expedited review status during the IDE phase, the responsible ODE review division will promptly provide a copy of the expedited review decision letter to the PMA Staff and DBM. Early and frequent interaction between ODE and DBM is critical to identify appropriate sites for inspection and validation of the submission's clinical data and information. DBM will develop, schedule, or assess the results of these inspections prior to the submission of the expedited review PMA application, whenever possible.

9. The POS will include DBM on the distribution list for all PMA boilerplate letters related to originals and panel-track supplements. In addition, the PMA Staff will maintain the bioresearch monitoring information in the PMA database. The database will include the initials of the DBM point-of contact and information on the inspectional status including specific site information and the outcome of the inspections.

10. DBM will be responsible for communicating the inspectional findings to the ODE review division and for providing copies of all bioresearch monitoring actions and recommendations regarding PMAs, PDPs, and panel-track supplements to both the PMA Staff and the reviewing Division within ODE. This will include copies of all requests for inspection, inspectional findings, and any actions taken such as issuance of a warning letter. These measures will aid in determining whether additional inspections or other actions are needed. The PMA application number or PDP number will be on all documents provided to ODE to facilitate tracking of the information.

11. The DBM will prepare a Summary of Findings memo referencing each site inspection. This memo will include a compliance assessment of the inspectional findings at each site and any subsequent responses by the regulated firm/individual or their representative.

    Because of resource limitations, DBM may not complete the inspectional process by the time ODE is prepared to issue a final decision letter. If this occurs, the ODE will consider any available bioresearch monitoring information in its final decision on a PMA, PDP, or panel-track supplement.

    If ODE has completed the review, but the bioresearch monitoring audit has revealed a serious problem which impacts on the evaluation of the safety and effectiveness of the device, ODE will delay the final decision until the problem is resolved.

    The DBM will provide the Summary of Findings memo to ODE for inclusion in the PMA or PDP administrative record at least 5 days prior to ODE's final decision whenever possible. This will ensure that ODE properly considers all the DBM inspectional findings prior to the final decision.

If you have questions regarding any aspects of the interoffice agreement or how the agreement will impact upon the applications in your division, please contact the PMA Staff at (301) 594-2186. Any questions from the regulated industry regarding the PMA bioresearch monitoring program other than questions relating to ODE procedures and responsibilities, should be referred to DBM at (301) 594-4718.

Effective Date

This policy is effective immediately.

_____
Susan Alpert, Ph.D., MD
Director
Office of Device Evaluation

_____
Lillian J. Gill
Director
Office of Compliance

Attachment A

What is the Bioresearch Monitoring Program?

INTRODUCTION

The Food and Drug Administration's (FDA) bioresearch monitoring program was established in 1977 by a task force which included representatives from the drug, biologics, medical device, veterinary medicine, and food areas. The need for such a program was evident in a survey of the conduct of studies involving FDA-regulated products by the FDA field inspection operation between 1972 and 1974. Following a review of the inspectional findings, the Congress mandated that FDA develop and implement an agency-wide program.

The bioresearch monitoring program at the Center for Devices and Radiological Health (CDRH) was expanded in June 1992. In May 1993 the Bioresearch Monitoring Branch became the Division of Bioresearch Monitoring in the reorganization of the Office of Compliance. The Division of Bioresearch Monitoring is responsible for monitoring sponsors, institutional review boards, clinical investigators, and nonclinical laboratories involved in the testing of investigational devices.

PROGRAM OBJECTIVES

The objectives of the bioresearch monitoring program are twofold: (1) to ensure the quality and integrity of data and information submitted in support of investigational and marketing clearance applications or submissions [IDEs, PMAs, and 510(k)s]; and (2) to ensure that human subjects taking part in investigations are protected from undue hazard or risk. DBM is also charged with the implementation of the FDA's Application Integrity Policy (AIP) for medical devices and radiological health products.

The program objectives are achieved by several means which are discussed in the program functions and inspection program sections below.

PROGRAM FUNCTIONS

The Division of Bioresearch Monitoring's (DBM) operations are directed toward several program areas. These include (1) audits of clinical data contained in PMA and some 510(k) submissions, ordinarily prior to approval; (2) audits of IDE submissions; (3) inspections of nonclinical laboratories that perform medical device-related safety testing; (4) inspections of Institutional Review Boards that monitor investigational device studies; (5) enforcement of the prohibition against commercialization of investigational devices; (6) providing education, training and guidance to regulated industry and (7) implementation of the FDA's Application Integrity Policy (AIP). Descriptions of some of these activities are summarized below:

PMA data audits are conducted through comprehensive on-site inspections by FDA field office staff. Source data generated and collected by clinical investigators are compared with the data and information submitted by the sponsor to FDA in support of such applications. These audits help to ensure the quality and integrity of the information used by the FDA to render safety and effectiveness decisions. Additionally, FDA field staff review the appropriate records to ensure protection of the rights and welfare of the clinical research subjects participating in these studies. Where clinical data exists in 510(k) submissions, assignments may be issued requesting audits of that data.

When indicated, inspections of clinical investigators participating in IDE studies are conducted.

Good Laboratory Practice (GLP) inspections are undertaken to investigate compliance with regulations promulgated under 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. Compliance with these regulations is intended to ensure the quality and integrity of safety data obtained from animal studies submitted to FDA.

Surveillance information received from district offices, the public, the industry, and other sources related to commercialization or promotion of investigational devices is also reviewed. If the advertisements or articles deviate from the requirements set forth in 21 CFR 812.7 (Prohibition of promotion and other practices), DBM follows up by means of a letter to the promoter or a request for inspection of the responsible party.

Implementation of the FDA's Application Integrity Policy involves investigations of sponsors that are suspected of submitting false or misleading data to the FDA. It also includes the review, evaluation, and monitoring of validity assessments required to be completed by sponsors found guilty of fraudulent activities.

The regulations enforced by the bioresearch monitoring program for medical devices are found in four sections of the CFR:

21 CFR 812 -Investigational Device Exemptions
21 CFR 50 - Protection of Human Subjects
21 CFR 56 - Institutional Review Boards
21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies

INSPECTION PROGRAMS

FDA's inspection programs include two types of assignments: routine inspections and directed inspections (sometimes termed "for cause"). The routine assignments include inspections of clinical investigators, sponsors, IRBs, or non-clinical laboratories that are randomly selected for coverage under one of four compliance programs. These assignments are issued to monitor adherence to FDA regulations.

A directed inspection is requested when some specific problem has been identified within one or all entities of the program. The problem may be observed during the review of sponsor submissions related to ongoing IDE investigations or following evaluation of clinical data submitted in a PMA or 510(k) application. Verbal or written complaints from patients, physicians, or competitors may also result in a directed inspection. Inspections issued for PMA data audits also fall into this category.

Deviations revealed during inspections are presented in writing and discussed with the responsible individual at the close of the inspection. Once an inspection has been completed, an establishment inspection report (EIR) is prepared and submitted by the district office. This report is then reviewed and classified by DBM.

Classifications assigned to inspections indicate whether or not the establishment is operating in compliance with the regulations. The classification scheme used by FDA is as follows:

NAI - No Action Indicated
VAI - Voluntary Action Indicated
OAI - Official Action Indicated

Depending upon the assigned classification, DBM may issue an untitled letter or warning letter based upon the severity of the deviations. These letters are intended to communicate the FDA's position on a matter, but do not commit the FDA to take further enforcement action. They are issued for the purpose of achieving voluntary compliance with the expectation that a majority of firms and individuals will comply with the regulations and implement corrective actions to prevent recurrence of the deviations.

When deviations are flagrant or significantly impact the quality and/or integrity of the research data, various actions have been used by the division to achieve compliance in the bioresearch monitoring program area. Data audits have resulted in the division's recommendation to invoke the Application Integrity Policy against the sponsor or reject clinical research data used to support a PMA. Inspections of violative IRBs have resulted in administrative sanctions that suspend the institution's authority to approve new studies and/or add new subjects to existing studies.

For additional information about the bioresearch monitoring program in CDRH, contact:

Charma A. Konnor, R.Ph., Director
Division of Bioresearch Monitoring (HFZ-310)
Office of Compliance
Center for Devices and Radiological Health
2094 Gaither Road Rockville, Maryland 20850
Telephone (301) 594-4718